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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Rec PCT/PTO 27 SEP 2004

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Applicant's or agent's file reference 2FPO-02-09	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. <b>PCT/KR2002/000595</b>	International filing date (day/month/year) <b>03 APRIL 2002 (03.04.2002)</b>	Priority date (day/month/year)
International Patent Classification (IPC) or national classification and IPC  <b>IPC7 A61K 31/47</b>		
Applicant  <b>CHEMON INC. et al</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets, including this cover sheet.
- ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:
- I ☒ Basis of the report
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

Date of submission of the demand  03 NOVEMBER 2003 (03.11.2003)	Date of completion of this report  27 MAY 2004 (27.05.2004)
Name and mailing address of the IPEA/KR  Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer  LEE, HYUN SONG  Telephone No. 82-42-481-5606 

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/KR2002/000595

## I. Basis of the report

### 1. With regard to the elements of the international application:\*

- ☐ the international application as originally filed
- ☒ the description:  
 pages 2-5, 9-12, 15-39, 41-49, as originally filed  
 pages \_\_\_\_\_, filed with the demand  
 pages 1, 6, 7, 8, 13, 14, 40, filed with the letter of 12/05/2004
- ☒ the claims:  
 pages \_\_\_\_\_, as originally filed  
 pages \_\_\_\_\_, as amended (together with any statement) under Article 19  
 pages \_\_\_\_\_, filed with the demand  
 pages 50-52, filed with the letter of 12/05/2004
- ☐ the drawings:  
 pages \_\_\_\_\_, as originally filed  
 pages \_\_\_\_\_, filed with the demand  
 pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_
- ☐ the sequence listing part of the description:  
 pages \_\_\_\_\_, as originally filed  
 pages \_\_\_\_\_, filed with the demand  
 pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

### 2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language English which is

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☒ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

### 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

### 4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages \_\_\_\_\_
- ☐ the claims, Nos. \_\_\_\_\_
- ☐ the drawings, sheet \_\_\_\_\_

### 5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\* Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.

# INTERNATIONAL PRELIMINARY EXAMINATION

International application No.

PCT/KR2002/000595

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Claims 1-6	YES
	Claims	NO
Inventive step (IS)	Claims 1-6	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-6	YES
	Claims	NO

### 2. Citations and explanations (Rule 70.7)

The following documents are referred to:

D1: US-A-4943577

D2: US-A-5372813

D3: US-A-6166205

1. D1 discloses a piperazinyl quinoline compound having an alkyl piperazinyl side chain for the treatment of a mental disorder. D3 discloses a piperazinyl quinoline compound having an imidazole side chain useful as a dopamine (D4) antagonist. Both D1 and D3 have the same structural moiety but have differential side chains, compared to the present claims 1-6. The most relevant compound disclosed in D2 cannot destroy the novelty of claims 1-6 because of the claims amended by the letter of 12/05/2004. Accordingly, the subject matter of claims 1-6 seems to be novel (Article 33(2) PCT).

2. The closest state of the art appears to be represented by D2 which discloses a method for the measurement of serotonin uptake sites in a sample using piperazinyl quinoline. The chemical structural difference between D2 and the present application is the position of the side chain on quinoline. The compound in D2 has side chains at 3, 5, 7, and 8 positions of quinoline, while the present compound has them at 3, 4, and 6 positions. The addition of the side chain to quinoline moiety does not require a special reaction scheme. Consequently, the inventive step of the present application should be considered based on the effect resulting from the substitution of side chains on quinoline. Compared to D2, the present compounds show an outstanding affinity for the serotonin transfer (e.g. the affinity of the compound shown in Example 10 is 10 times as high as that of the compound with H at 4 position of quinoline). Consequently, the inventive step of claims 1-3 can be acknowledged. The subject matter of claims 4-6 is a method for preparing a compound and a pharmaceutical usage. The inventive step of claims 4-6 can be acknowledged because the inventive step of the present compound is approved.

Thus, claims 1-6 involve an inventive step and meet the requirement of Article 33(3) PCT.

The present application is considered to meet the criteria of industrial applicability (Article 33(4) PCT).

Rec'd PCT/PTO 27 SEP 2004

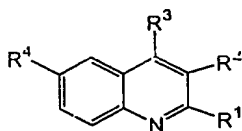
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IPEA/KR 12.05.2004

QUINOLINE DERIVATIVES, THEIR PREPARATION AND PHARMACEUTICAL  
COMPOSITIONS COMPRISING THE SAME

TECHNICAL FIELD

5           The present invention relates to quinoline derivatives  
represented by in formula 1 as below. More specifically, the  
present invention relates to quinoline derivatives and their  
pharmaceutically acceptable salts that interrupt the  
reuptake of serotonin into presynaptic neuron and thus  
10   increase the concentration of serotonin in synapse. The  
present invention also includes the process for preparing  
the said compounds of formula 1 and their pharmaceutical  
compositions to prevent or treat serotonin-related mental  
disorders comprising the said compounds as effective  
15   ingredients.

Formula 1



wherein,

20   R<sup>1</sup> is piperazinyl, 2-methylpiperazinyl, perhydrodiazepinyl  
or N-methyl-N-(2-N'-methylamino)ethylamine;

R<sup>2</sup> is H, halogen atom, C<sub>1</sub>~C<sub>4</sub> alkyl or C<sub>1</sub>~C<sub>4</sub> haloalkyl;

R<sup>3</sup> is H, halogen atom, vinyl or furanyl group; and

R<sup>4</sup> is halogen atom or nitro group.

BACKGROUND ART

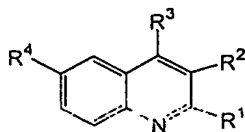
nitro-2-(piperazin-1-yl)quinoline is administered to depression-induced mice and 0.5% dimethylsulfoxide (DMSO) is administered to them as a control;

Figure 2B is a graph illustrating the anti-depression effect obtained by measuring of immobility time using a tail suspension test wherein 1 mg/kg or 10 mg/kg of 4-chloro-6-nitro-2-piperazine is administered to depression-induced mice and 0.5% dimethylsulfoxide (DMSO) is administered to them as a control.

#### DISCLOSURE OF INVENTION

The present invention provides quinoline derivatives and their pharmaceutical acceptable salt represented by the following formula 1:

Formula 1



wherein,

R<sup>1</sup> is piperazinyl, 2-methylpiperazinyl, perhydrodiazepinyl or N-methyl-N-(2-N'-methylamino)ethylamine group;

R<sup>2</sup> is H, halogen atom, C<sub>1</sub>~C<sub>4</sub> alkyl or C<sub>1</sub>~C<sub>4</sub> haloalkyl;

R<sup>3</sup> is H, halogen atom, vinyl or furanyl group; and

R<sup>4</sup> is halogen atom or nitro group.

More preferably,

R<sup>1</sup> is 2-methylpiperazinyl, perhydrodiazepinyl, or N-

methyl-N-(2-N'-methylamino)ethylamine group;

R<sup>2</sup> is H, bromine, methyl, ethyl, propyl, chloropropyl or fluoropropyl group;

R<sup>3</sup> is H, chlorine, bromine, iodine, vinyl or 2-furanyl group; and

R<sup>4</sup> is chlorine, bromine or nitro group.

Most preferably, examples of the compounds represented by the chemical formula 1 include the following table 1:

Table 1

Example	Compound	Formula
1	3-methyl-6-nitro-2-(piperazin-1-yl)quinoline	
2	3-ethyl-6-nitro-2-(piperazin-1-yl)quinoline	
3	6-nitro-2-(piperazin-1-yl)-3-propylquinoline	
4	3-(3-chloropropyl)-6-nitro-(piperazin-1-yl)quinoline	
5	6-iodo-2-(piperazin-1-yl)quinoline	
6	6-bromo-2-(piperazin-1-yl)quinoline	
7	6-chloro-2-(piperazin-1-yl)quinoline	

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8	3-(3-fluoropropyl)-6-nitro-2-(piperazin-1-yl)quinoline	
9	3-bromo-6-nitro-2-(piperazin-1-yl)quinoline	
10	4-chloro-6-nitro-2-(piperazin-1-yl)quinoline	
11	4-bromo-6-nitro-2-(piperazin-1-yl)quinoline	
12	4-iodo-6-nitro-2-(piperazin-1-yl)quinoline	
13	6-nitro-2-(piperazin-1-yl)-4-vinylquinoline	
14	4-(2-furanyl)-6-nitro-2-(piperazin-1-yl)quinoline	
15	2-(3-methylpiperazin-1-yl)-6-nitroquinoline	
16	2-(N-methyl-N-(2-N'-methylamino)ethyl)amino-6-nitroquinoline	
17	2-perhydrodiazepin-1-yl-6-nitroquinoline	

The present invention further includes solvated compounds and hydrates prepared by use of the quinoline derivatives of formula 1 and their pharmaceutically acceptable salts.

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tributyl(vinyl)tin or tributyl(2-furanyl)tin in the presence of palladium catalyst to introduce vinyl or furanyl at 4-position of compounds of formula 6; and

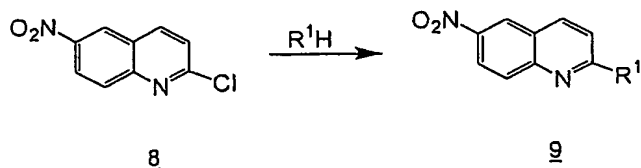
- 5           b) treating thus obtained mixture with acid compounds.

Preferably, the Stille reaction is carried out from 90 °C to 120 °C under inert gas, e.g., N<sub>2</sub>(g).

- 10           In this case, it is possible to prepare the compounds substituted with aryl, heteroaryl and aryl group besides vinyl and furanyl group.

- 15           In accordance with yet another aspect of the present invention, there is provided a method for preparing an 2-(3-methylpiperazin-1-yl)-6-nitroquinoline, 2-(N-methyl-N-(2-N'-methylamino)ethylamino)-6-nitroquinoline and 2-perhydrodiazepin-1-yl-6-nitroquinoline, represented by the following reaction scheme 4:

- 20           Reaction Scheme 4



wherein,

R<sup>1</sup> is 2-methylpiperazinyl, N-methyl-N-(2-N'-methylamino)ethylamine or perhydrodiazepinyl group.



As shown, the compounds of formula 9 including an 2-(3-methylpiperazin-1-yl)-6-nitroquinoline, 2-(N-methyl-N-(2-N'-methylamino)ethylamino)-6-nitroquinoline and 2-perhydrodiazepin-1-yl-6-nitroquinoline is prepared by reacting 2-chloro-6-nitroquinoline of formula 8 with 2-methylpiperazine, N-methyl-N-(2-N'-methylamino)ethylamine or perhydrodiazepine.

In accordance with a further aspect of the present invention, there is provided a pharmaceutical composition comprising the compounds of formula 1 as an effective ingredient to prevent or treat mental disorder caused by serotonin.

Concretely, the quinoline derivatives of the invention may be utilized to prevent or treat mental disorders, especially to depression.

In a preferable embodiment of the present invention, the brain tissue was gently isolated from a mouse, grounded, and then the biological activity against SERT was measured in a variety of concentration. As a result, the compounds of the present invention shows a much higher  $K_i$  value than that of the already commercialized Fluoxetine and a similar value to that of Paroxetine. As shown table 3, especially, 4-chloro-6-nitro-2-piperazin-1-yl-quinoline shows an excellent binding affinity over ten times than 6-nitro-2-

8.0 Hz, 1H), 4.08 (t,  $J = 6.9$  Hz, 2H), 3.24-3.38 (m, 5H),  
2.68 (s, 3H).

$^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ )  $\delta$  153.2, 143.5, 143.2, 139.5, 126.2,  
124.3, 119.9, 118.6, 112.6, 47.9, 44.6, 38.1, 32.7.

5

**EXAMPLE 17 : Preparation of 2-perhydrodiazepin-1-yl-6-nitro-quinoline**

10 In 10 ml of DMF, 2-chloro-6-nitroquinoline (500 mg,  
2.40 mmol) was dissolved, added perhydrodiazepine (894 mg,  
7.20 mmol) at room temperature, and then reacted at 80 °C for  
5 hours. After the completion of the reaction, the mixture  
was cooled to room temperature, added water to produce a  
precipitate. The precipitate was isolated by filtration,  
15 washed with 50 ml of water, and then dried over for 3 hours  
in vacuo to give the desired product as a yellowish solid  
(602 mg, 2.21 mmol, 92%).

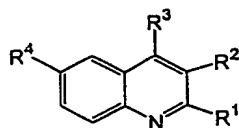
20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.52 (d,  $J = 2.6$  Hz, 1H), 8.27 (dd,  $J$   
= 9.3, 2.7 Hz, 1H), 7.93 (d,  $J = 9.2$  Hz, 1H), 7.62 (d, 9.4  
Hz, 1H), 6.97 (d,  $J = 9.0$  Hz, 1H), 3.87-3.93 (m, 4H), 3.11  
(t,  $J = 5.3$  Hz, 2H), 2.89 (t,  $J = 5.9$  Hz, 2H), 2.22 (br s,  
1H), 1.91-2.03 (m, 2H);

25  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  157.1, 150.5, 139.4, 137.7, 125.4,  
123.6, 122.2, 119.7, 46.92, 46.03, 45.41, 37.2, 27.5.

WHAT IS CLAIMED IS

1. A quinoline derivative of formula 1, or pharmaceutically acceptable salt of the same:

formula 1



wherein,

R<sup>1</sup> is piperazinyl, 2-methylpiperazinyl, perhydrodiazepinyl or N-methyl-N-2-N'-methylamino)ethylamine group;

10 R<sup>2</sup> is H, halogen atom, C<sub>1</sub>~C<sub>4</sub> alkyl or C<sub>1</sub>~C<sub>4</sub> haloalkyl;

R<sup>3</sup> is H, halogen atom, vinyl or furanyl group; and

R<sup>4</sup> is halogen atom or nitro group

with the proviso that

when R<sup>1</sup> is piperazinyl or 2-methylpiperazinyl;

R<sup>3</sup> is H; and

R<sup>4</sup> is nitro group,

R<sup>2</sup> is not H, halogen atom, C<sub>1</sub>~C<sub>3</sub> alkyl, or C<sub>1</sub>~C<sub>3</sub> haloalkyl.

2. The derivative of claim 1, wherein R<sup>1</sup> is 2-methylpiperazinyl, perhydrodiazepinyl or N-methyl-N-2-N'-methylamino)ethylamine;

15 R<sup>2</sup> is H, bromine, methyl, ethyl, chloropropyl or fluoropropyl;

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R<sup>3</sup> is H, chlorine, bromine, iodine, vinyl or 2-furanyl group; and

R<sup>4</sup> is chlorine, bromine, iodine, or nitro group with the proviso that

when R<sup>1</sup> is 2-methylpiperazinyl;

R<sup>3</sup> is H; and

R<sup>4</sup> is nitro group,

R<sup>2</sup> is not H, bromine, methyl or ethyl.

3. The derivative of claim 1, wherein the derivative is selected from the group consisting of:

3-(3-chloropropyl)-6-nitro-2-piperazin-1-yl-quinoline;

3-(3-fluoropropyl)-6-nitro-2-piperazin-1-yl-quinoline;

6-iodo-2-piperazin-1-yl-quinoline;

6-bromo-2-piperazine-1-yl-quinoline;

6-chloro-2-piperazin-1-yl-quinoline;

4-chloro-6-nitro-2-piperazin-1-yl-quinoline;

4-bromo-6-nitro-2-piperazin-1-yl-quinoline;

4-iodo-6-nitro-2-piperazin-1-yl-quinoline;

6-nitro-2-piperazin-1-yl-4-vinylquinoline;

4-(2-furanyl)-6-nitro-2-piperazin-1-yl-quinoline;

2-(N-methyl-N-(2-N'-methylamino)ethyl)amino-6-nitroquinoline; and

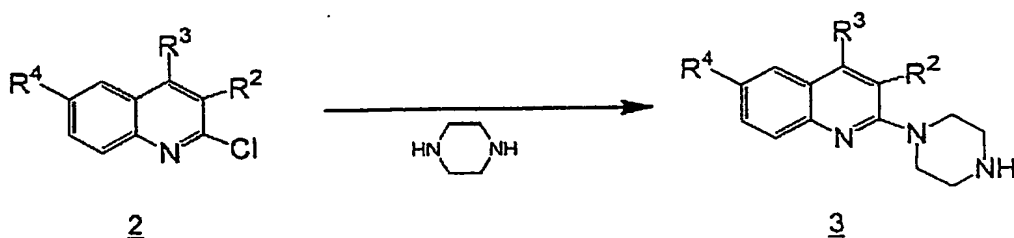
2-perhydrodiazepin-1-yl-6-nitroquinoline.

4. A method for preparing a compound of formula 3, which

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comprises substituting a quinoline compound of formula 2 with piperazine to introduce a piperazinyl group at 2-position of the quinoline compound of formula 2:

Reaction Scheme 1



wherein,

R<sup>2</sup> is H, halogen atom, C<sub>1</sub>~C<sub>4</sub> alkyl or C<sub>1</sub>~C<sub>4</sub> haloalkyl;

R<sup>3</sup> is H, halogen atom, vinyl or furanyl group; and

R<sup>4</sup> is halogen atom or nitro group.

5. A pharmaceutical composition comprising the quinoline derivative of the formula 1 as an effective ingredient for preventing or treating serotonin-related mental disorder.

6. The composition of claim 1, wherein the mental disorder is a depression.